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An Investigation into the Synthesis of a Four-Armed Diamino Swallowtail

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AN INVESTIGATION INTO THE SYNTHESIS OF A FOUR-ARMED DIAMINO SWALLOWTAIL

by
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ABSTRACT
CHRISTOPHER CARTER BARNETT: An Investigation into the Synthesis of a Four-Armed Diamino Swallowtail
(Under the direction of Daniell Mattern)

Perylenebisimides (PBIs) complex with quadruplex DNA and may influence the formation of telomeres. PBIs with amine groups are ionized at neutral pH and therefore soluble in water [1]. Swallowtails are long alkyl chains usually attached to PBIs to inhibit self-aggregation by pi-stacking [2]. Past attempts to create a PBI with swallowtails containing extra nitrogens were unsuccessful due to purification issues and methylene connectors. The purpose of this research is to investigate the synthesis of a diamino swallowtail with a methine connector. The first step is to create 1,3-bis(dibenzylamino)propan-2-one by way of an S_N2 substitution reaction using 1,3-dichloroacetone and dibenzylamine [3]. The product was created using the Finkelstein reaction along with a second S_N2 substitution reaction [4]. The next step is the creation of an oxime to later be reduced into an amine [5]. Due to lack of time, the creation of the oxime was the furthest step reached. Nonetheless, the trials of this research give valuable insight into the possibility of creating the targeted swallowtails. If ultimately successful, these swallowtails could provide more insight into future research regarding PBI binding to G-quadruplex DNA.

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Chapter 1: Introduction and Background

Perylenebisimides, also known as PBIs, are organic compounds that can complex with quadruplex DNA. PBIs may also influence the formation of telomeres, which are regions of repetitive nucleotide sequences commonly found at the end of chromatids in cells. Telomeres are necessary for protecting the ends of the chromosome from deterioration or even fusion with neighboring chromosomes. Scientists have been able to show that telomeric repeats form quadruplex structures in DNA *in vitro* and also *in vivo*. The formation of telomeric quadruplexes decreases the activity of the enzyme telomerase, which is responsible for maintaining the length of telomeres and is also involved in nearly 85% of cancers. The formation of telomeric quadruplexes has become a very popular topic among scientists in the field of oncology and pharmaceuticals.

PBIs with amine groups are known for being ionized at a neutral pH, which causes PBIs to become soluble in water. One water-soluble PBI is the classic quadruplex binder N,N′-*bis*[2-(1-piperidino)ethyl]-3,4,9,10-perylenetetracarboxylic diimide, more commonly known as PIPER (Figure 1.1).

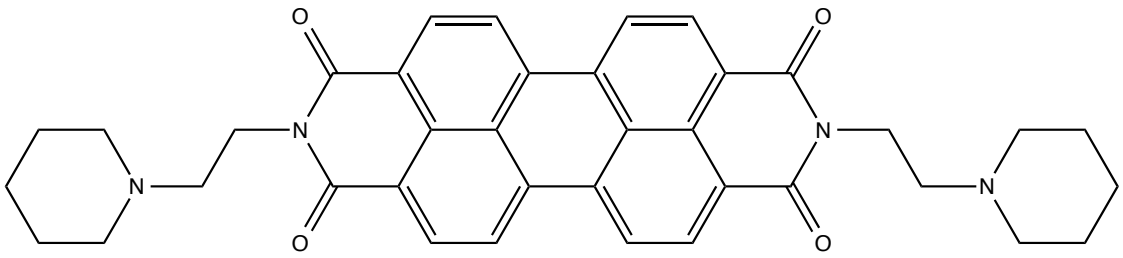

Figure 1.1 – PIPER is the classic quadruplex binder used in binding to G-quadruplex DNA.

In his 2013 Honors College Thesis *Polycationic Perylenebismides for G-Quadruplex Binding,* Andrew Matrick attempted to create a PBI with "swallowtails" featuring extra nitrogens to get multiple ionic charges. Such multiple ionic charges might increase the solubility as well as the DNA binding ability of the PBI [1]. Swallowtails are long alkane chains connected to the rest of the molecule at midchain; one is shown in Figure 1.2. PBIs like to self-aggregate through a process called pi-stacking. Swallowtails are attached to PBIs to keep the pi planes separated and inhibit aggregation, and thereby improving solubility [2]. Matrick was unable to successfully purify his target molecule, shown in Figure 1.3. One of the possible explanations for the difficulty in purification could be due to the PBI nitrogen attaching to a methylene instead of the bulkier methine of a normal swallowtail. The methine's extra steric profile might help keep the pi systems separated and make those PBIs more tractable.

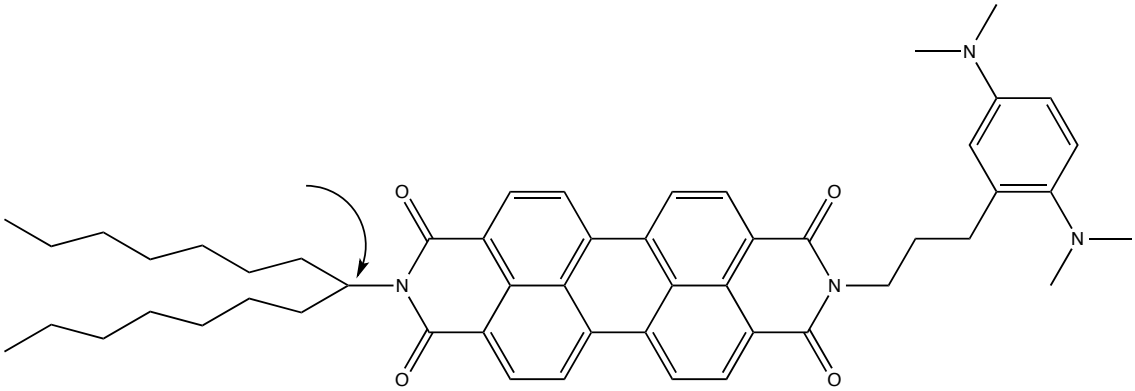

Figure 1.2 – The long carbon chain on the left side of this PBI molecule is an example of a swallowtail used to inhibit self-aggregation through pi-stacking.

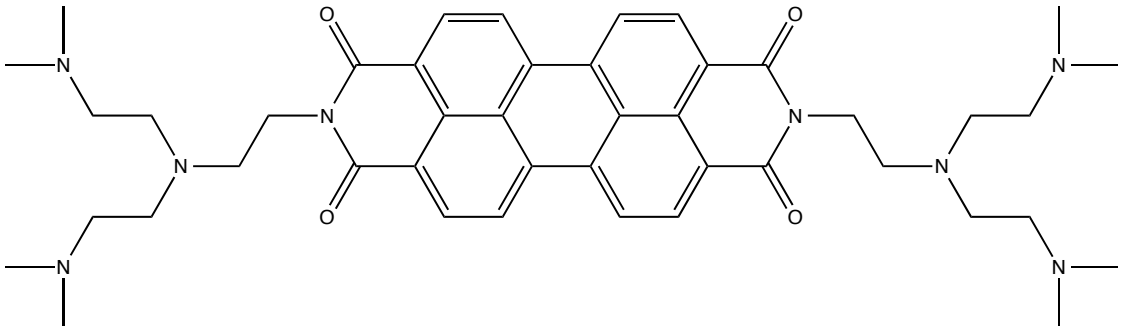

Figure 1.3 – Target molecule in Matrick thesis that could not be purified. The molecule features swallowtail-like structures attached to each end of the PBI [1].

The focus of this thesis is based primarily on continuing the research of Andrew Matrick by trying to create a four-armed diamino swallowtail with a methine connector and two nitrogens per tail. With the hopeful success of this molecule, similar tails can be designed featuring more nitrogens; however, if the process in creating the target tails is difficult, the problem could lie in the nitrogens themselves. The target molecule in this thesis is illustrated in Figure 1.4.

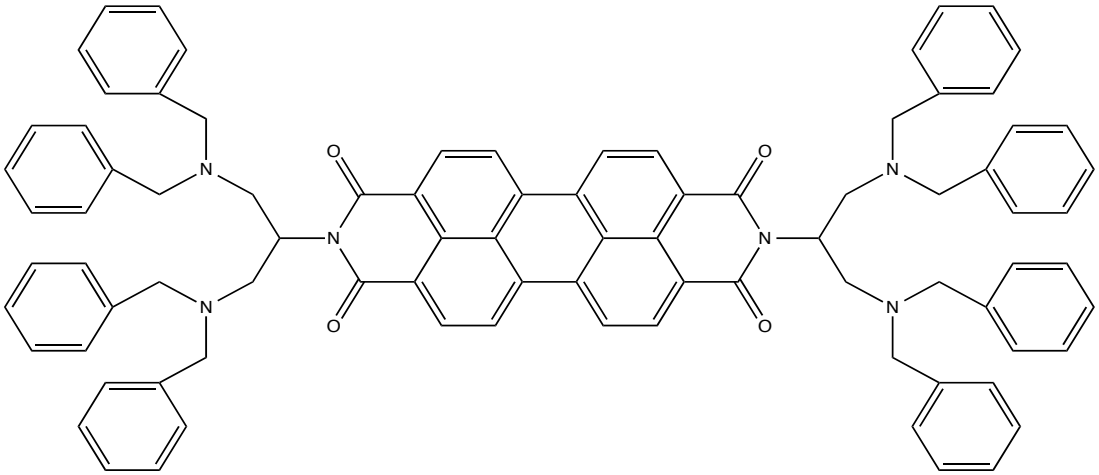

Figure 1.4 – Target molecule of this research endeavor.

Dibenzylamine tails were chosen instead of dihexylamine tails due to the molecule being easier to follow through thin layer chromatography and NMR

spectroscopy; the structures of these two tails are shown in Figure 1.5. In terms of TLC, dibenzylamine tails are better for the reaction because of the polarity of the molecule. The nitrogens have the same effect on polarity in each of the molecules; however, the aromatic hydrocarbons of the dibenzylamine tails are more polar than the saturated hydrocarbons of the dihexylamine tails. The polarity is important in terms of the absorptive ability of the compound to the silica and also the R_f value. Polar compounds have smaller R_f values, which means the compounds do not move as far on the silica plate. When analyzing the ^1H NMR spectrums of the two tails, the dibenzylamine tails are easier to follow due to the phenyl hydrogens creating peaks in the aromatic region between 7 ppm and 8 ppm and the methylene hydrogens creating simple singlet peaks between 3 ppm and 4 ppm.

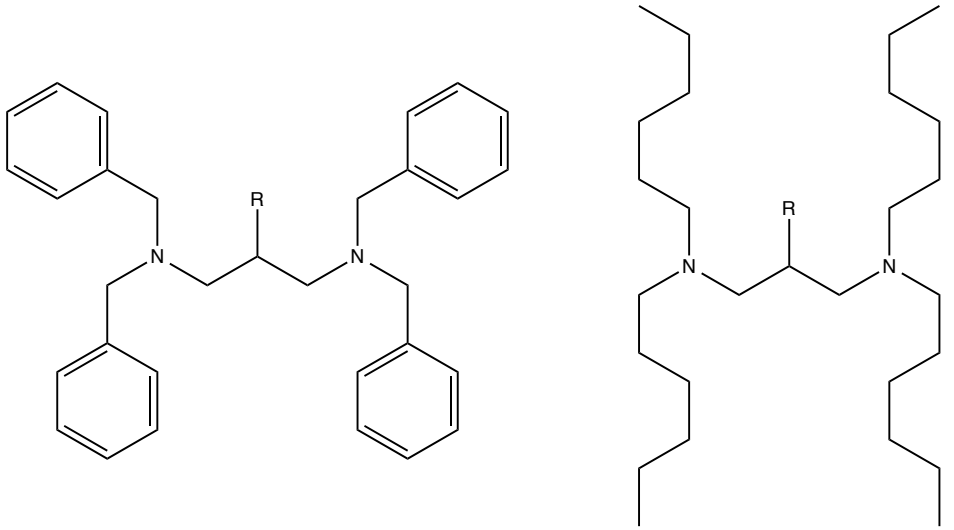

Figure 1.5 – Structures of dibenzylamine swallowtails and dihexylamine swallowtails

The first step in creating this molecule is creating the diamino swallowtails. The process begins by reacting 1,3-dichloroacetone with dibenzylamine in tetrahydrofuran (THF) with triethylamine to form 1,3-bis(dibenzylamino)propan-2-one by nucleophilic

substitution. The reaction scheme is shown in Figure 1.6.

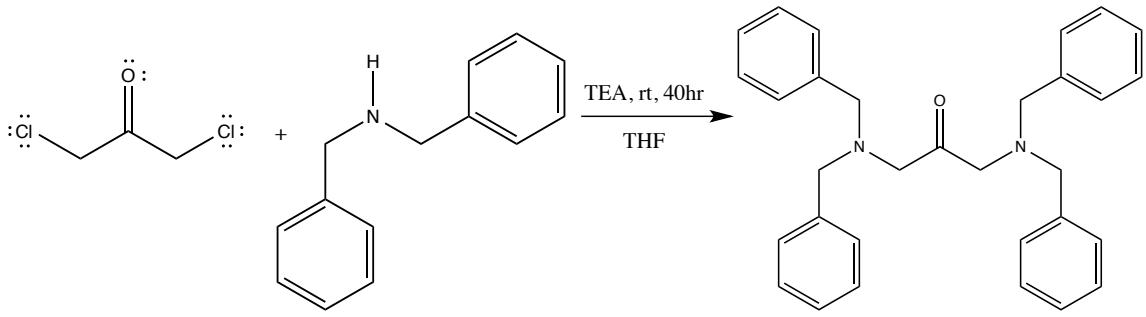

Figure 1.6 – Reaction scheme of 1,3-dichloroacetone with dibenzylamine in THF to form 1,3-bis(dibenzylamino)propan-2-one.

A possible side reaction exists: when a ketone reacts with a secondary amine, the product formed is an enamine, which is shown in Figure 1.7.

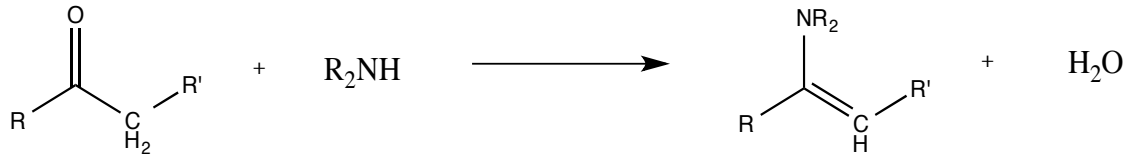

Figure 1.7 – Basic formation of enamine by nucleophilic addition of the secondary amine followed by elimination.

Nucleophilic substitution occurs when a nucleophile, a species that is an electron donor, attacks the backside of the electrophile, a species that is electron acceptor, and replaces a leaving group that was previously attached to the electrophile. In an S_N2 substitution, the backside attack of the nucleophile and the departure of the leaving group occur simultaneously. Below is the mechanism of the desired S_N2 substitution of dibenzylamine onto 1,3-dichloroacetone (Figure 1.8).

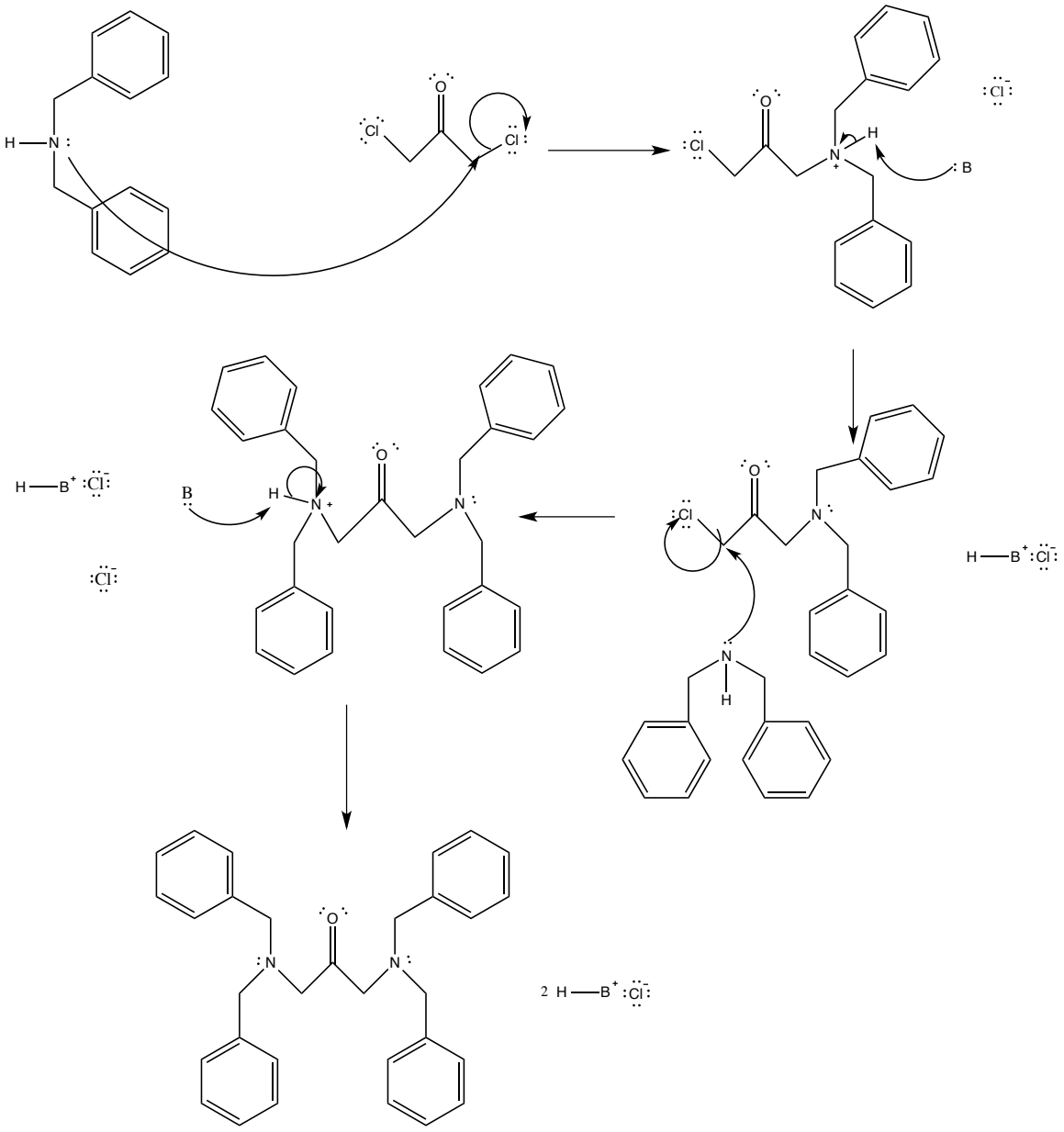

Figure 1.8 – Electron pushing mechanism of the S_N2 substitution involving dibenzylamine and 1,3-dichloroacetone.

I could find no literature procedure for the S_N2 substitution involving both 1,3-dichloroacetone and dibenzylamine; however, Burrows and associates were able to successfully perform a similar, single S_N2 substitution involving chloroacetone and dibenzylamine (Figure 1.9) [3]. With dibenzylamine serving as the nucleophile, the

group was successfully able to substitute the dibenzylamine onto the acetone by displacing the chlorine atom.

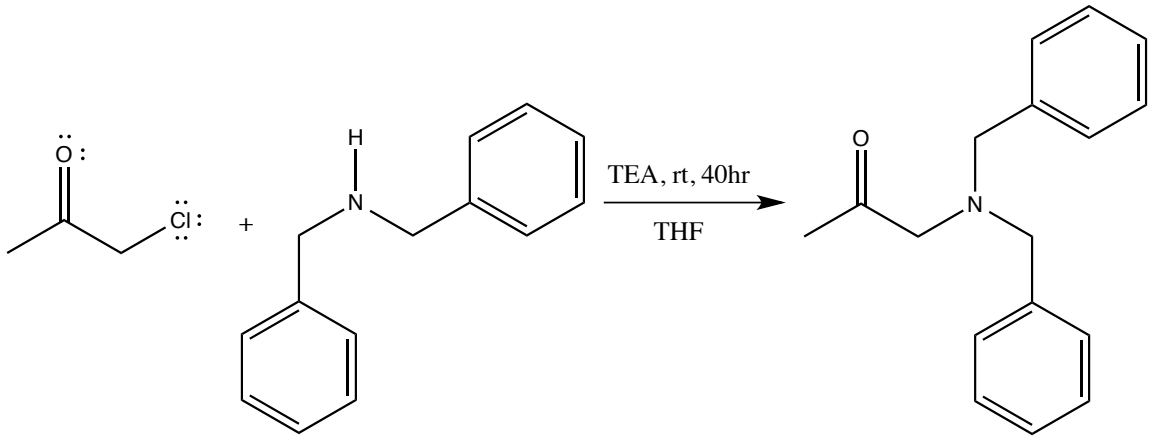

Figure 1.9 – Reaction scheme of Burrows and associates model S_N2 substitution reaction.

Using similar conditions, it might be possible to displace the two chlorines in 1,3-dichloroacetone with two dibenzylamines to form 1,3-bis(dibenzylamino)propan-2-one.

Rambabu Sankranti, a Ph.D. candidate at the University of Mississippi, suggested another set of conditions for forming 1,3-bis(dibenzylamino)propan-2-one. His suggestion involves two sequential S_N2 substitution reactions. The first reaction would form 1,3-diiodoacetone through a Finklestein reaction, and then the second reaction would add dibenzylamine in acetonitrile with potassium carbonate as base. A Finklestein reaction is an S_N2 reaction that involves the exchange of one halogen for another.

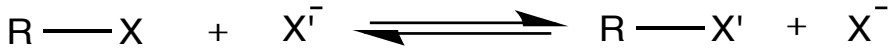

Figure 1.10 – Finklestein reaction. Normally X would be chlorine or bromine, and X' would be iodine.

The classic Finklestein reaction involves the conversion of an alkyl chloride or alkyl bromide into an alkyl iodide by treatment with a solution of sodium iodide or potassium iodide in acetone [4]. Although the Finklestein reaction is in equilibrium according to the

equation, the solvent is the key that drives this reaction towards to the products. Sodium iodide is very soluble in acetone, while sodium chloride and sodium bromide are not. As the iodide ions from sodium iodide displace the chlorides or bromides of the alkyl groups, either sodium chloride or sodium bromide form and precipitate out of the reaction causing the transformation to become irreversible, thus driving the reaction towards the products.

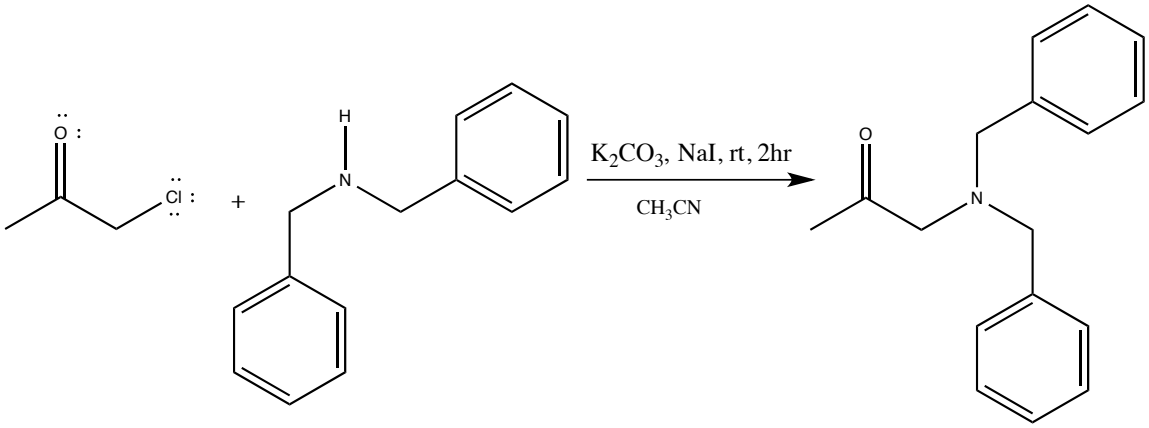

Figure 1.11 – Reaction scheme of Sankranti's route that suggests two S_N2 substitution reactions.

The goal of Sankranti's suggested route was shorter reaction time and possible higher yields. To test his suggestion, a model reaction was done under suggested conditions involving chloroacetone and dibenzylamine in acetonitrile to determine if the two sequential S_N2 substitutions would occur. Acetonitrile is an appropriate substitute for acetone because sodium iodide is also soluble in acetonitrile, while sodium chloride and sodium bromide are not. Theoretically in this case, the Finklestein reaction should proceed to completion with sodium chloride precipitating out prior to the second S_N2 substitution reaction. If the model reaction is successful, it is possible to substitute chloroacetone for 1,3-dichloroacetone in hopes of obtaining 1,3-

bis(dibenzylamino)propan-2-one. In order to maximize yields and lower reaction times, the two model reactions will be compared to determine the best route to obtain 1,3-bis(dibenzylamino)propan-2-one.

After the successful formation of 1,3-bis(dibenzylamino)propan-2-one, the next step in creating the diamino swallowtail amines is to convert the ketone carbonyl into an oxime, followed by reduction to a 2° amine using sodium bis(2-methoxyethoxy) aluminum hydride, also known as Red-Al. Using a procedure from a paper by Wescott and Mattern, the reaction calls for the use of a ketone, in this case the 1,3-bis(dibenzylamino)propan-2-one, to be treated with hydroxylamine hydrochloride, while being lightly heated [5]. The reaction scheme is shown in Figure 1.12.

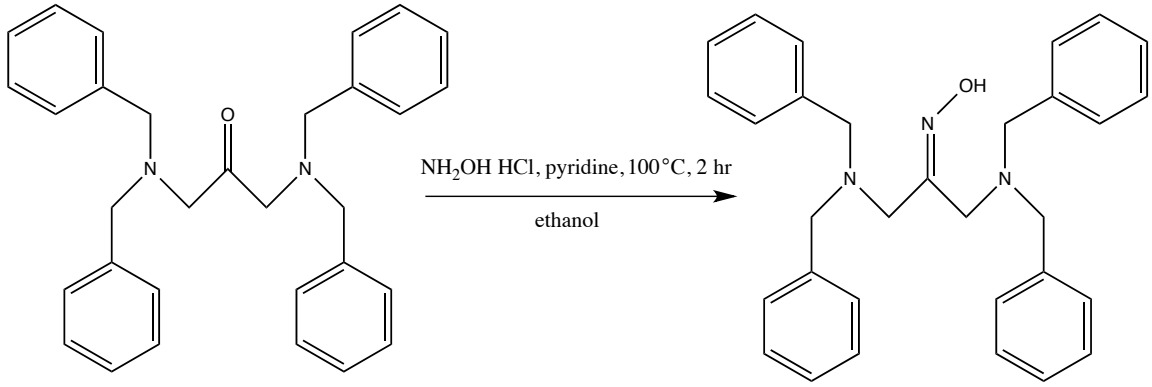

Figure 1.12 – Reaction scheme for formation of oxime from 1,3-bis(dibenzylamino)propan-2-one.

The next step would be to reduce the oxime using Red-Al under reflux, giving an amine that would be used as the tails of the targeted molecule of the research. Below is the mechanism for formation of an oxime from a 1,3-bis(dibenzylamino)propan-2-one and hydroxylamine (Figure 1.13).

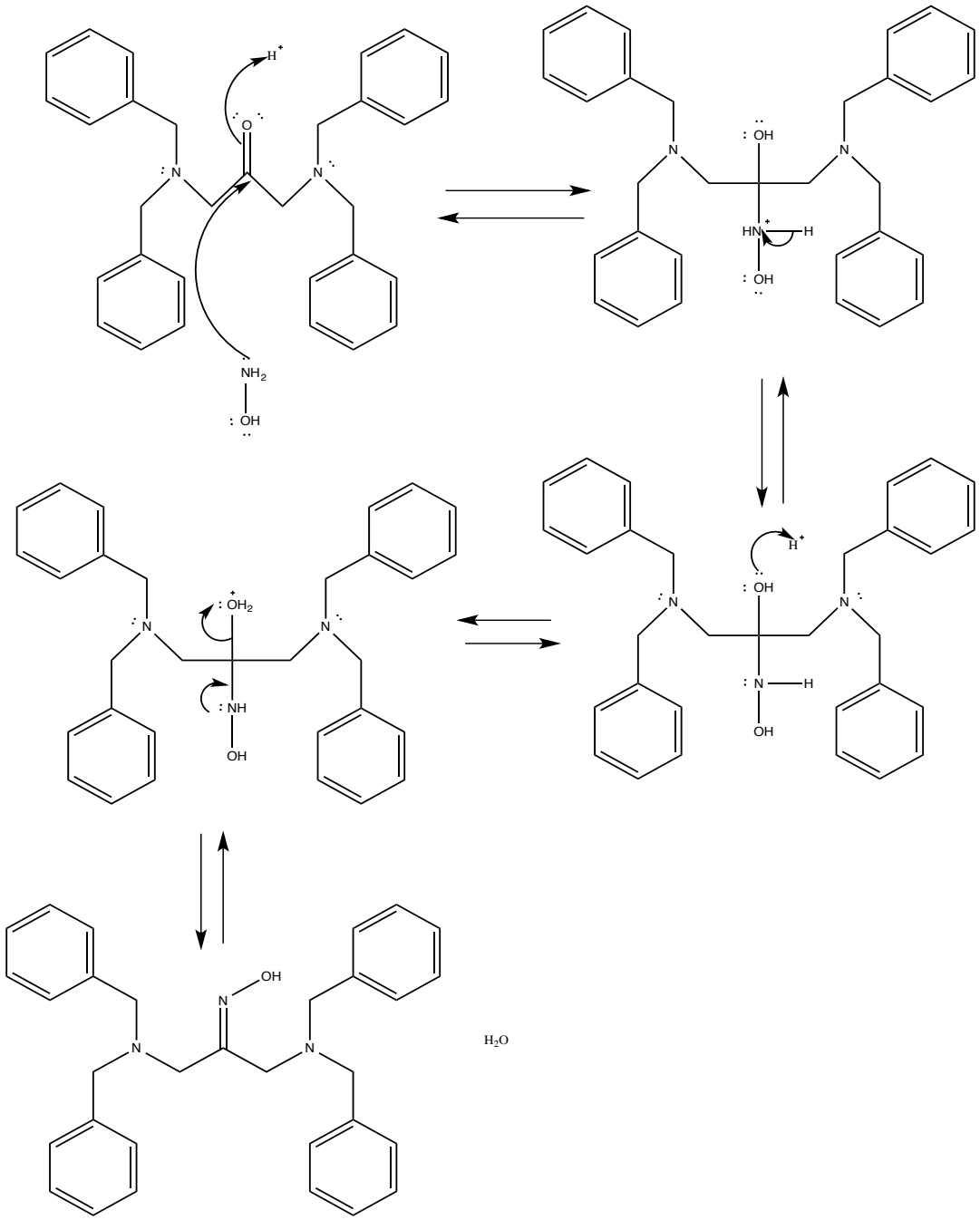

Figure 1.13 – Electron pushing mechanism of the formation of the oxime from 1,3-bis(dibenzylamino)propan-2-one.

Throughout the procedures from each of the previously mentioned journals and suggestions, thin layer chromatography and nuclear magnetic resonance spectroscopy were two essential techniques used to analyze data and determine the success of the

reactions. Thin layer chromatography, also known as TLC, is a useful technique for the separation and identification of compounds in mixtures. For the purpose of this research, TLC was used to follow the progress of reactions by monitoring the consumption of starting materials and the formation of products. TLC works through the separation of compounds between two phases based on the differences in solubility of compounds in two phases. In TLC, one phase is a mobile liquid solvent phase and the other phase is a stationary solid phase with a high surface area. The mobile phase primarily used in these experiments was a mixture of seven parts hexanes and three parts ethyl acetate. The stationary phase used in these experiments was silica (SiO_2) in the form of a thin layer on a sheet of metal foil.

Nuclear magnetic resonance spectroscopy, also known as NMR, is a technique used to distinguish between inequivalent nuclei such as ^{1}H or ^{13}C at different sites in a molecule. NMR spectroscopy can be used to determine the structure of complex molecules, to map out the electron distribution in molecules, to study the kinetics of chemical transformations, and even to nondestructively image internal organs in the human body. For the purposes of this research, proton NMR, abbreviated ^{1}H NMR, was used to determine the structures of the targeted molecules in each reaction.

Chapter 2: Experimental Procedures.

I. *Procedure for S_N2 Substitution involving Chloroacetone and Dibenzylamine using Triethylamine (TEA) in Tetrahydrofuran (THF)*

In a 25 mL round-bottom flask, dibenzylamine (1.006 g, 5.1 mmol) was dissolved in THF (7 mL). Chloroacetone (0.9437 g, 10.2 mmol) was added to the stirring solution followed by TEA (0.6173 g, 6.1 mmol). The reaction mixture was allowed to stir at room temperature for approximately 40 h. The reaction was followed using thin layer chromatography (TLC), and a spot was taken every ten hours. After 40 hours, the mixture was filtered via vacuum filtration, and the solid was washed with THF (3.90 mL). The resulting liquid was collected, and the solvent was removed using the rotary evaporator. The remaining oil was taken up in chloroform (4.50 mL) and washed with saturated, aqueous sodium bicarbonate (2.60 mL) and brine (2.60 mL). The combined organic layers were dried over magnesium sulfate, and the solvent was removed with the rotary evaporator. The remaining oil was purified with flash column chromatography using 7:3 hexanes/ethyl acetate as the eluting solvent, and a yield of 9% was obtained. A small sample of the remaining oil was dissolved in deuterated chloroform and analyzed by proton NMR.

II. *Procedure for S_N2 Substitution involving Chloroacetone and Dibenzylamine using Finkelstein Reaction and Potassium Carbonate*

In a 50 mL round-bottom flask, dibenzylamine (1.006 g, 5.1 mmol) was dissolved in acetonitrile (15 mL). Chloroacetone (0.9437 g, 10.2 mmol) was added to the stirring solution followed by sodium iodide (1.529 g, 10.2 mmol) and potassium carbonate (2.115 g, 15.3 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction was followed using TLC, and a spot was taken every 20 min. After 2 h, the mixture was filtered via vacuum filtration, and the solid was washed with acetonitrile (5 mL). The resulting liquid was collected, and the solvent was removed using the rotary evaporator. The remaining oil was taken up in chloroform (4.50 mL) and washed with saturated, aqueous sodium bicarbonate (2.60 mL) and brine (2.60 mL). The combined organic layers were dried over magnesium sulfate and filtered. The solvent was removed with the rotary evaporator. The remaining oil was purified with flash column chromatography using 7:3 hexanes/ethyl acetate as the eluting solvent, and a yield of 60% was obtained. A small sample of the remaining oil was dissolved in deuterated chloroform and analyzed by proton NMR.

III. *Procedure for S_N2 Substitution involving 1,3-Dichloroacetone and Dibenzylamine using Triethylamine (TEA) in Tetrahydrofuran (THF)*

In a 50 mL round-bottom flask, dibenzylamine (2.012 g, 10.2 mmol) was dissolved in THF (15 mL). 1,3-dichloroacetone (0.7123 g, 5.61 mmol) was added to the stirring solution followed by TEA (1.70 mL, 12.2 mmol). The reaction mixture was allowed to stir for approximately 40 h. The reaction was followed using TLC, and a spot

was taken every 10 h. After 40 h, the mixture was filtered via vacuum filtration, and the solid was washed with THF (10 mL). The resulting liquid was collected, and the solvent was removed using the rotary evaporator. The remaining oil was taken up in chloroform (10 mL) and washed with saturated, aqueous sodium bicarbonate (5 mL) and brine (5 mL). The combined organic layers were dried over magnesium sulfate and filtered. The solvent was removed using the rotary evaporator. The remaining oil was purified with flash column chromatography using 7:3 hexanes/ethyl acetate as the eluting solvent, and a yield of 6% was obtained. A small sample of the remaining oil was dissolved in deuterated chloroform and analyzed by proton NMR.

IV. *Procedure for S_N2 Substitution involving 1,3-Dichloroacetone and Dibenzylamine using the Finkelstein Reaction and Potassium Carbonate*

In a 100 mL round bottom flask, dibenzylamine (2.012 g, 10.2 mmol) was dissolved in acetonitrile (30 mL). 1,3-dichloroacetone (0.7123 g, 5.61 mmol) was added to the stirring solution followed by sodium iodide (1.682 g, 11.22 mmol) and potassium carbonate (3.524 g, 25.5 mmol). The reaction mixture was allowed to stir at room temperature for 12 h. The reaction was followed using TLC. The mixture was filtered via vacuum filtration, and the solid was washed with acetonitrile (10 mL). The resulting liquid was collected, and the solvent was removed using the rotary evaporator. The resulting oil was taken up in chloroform (10 mL) and washed with saturated, aqueous sodium bicarbonate (5 mL) and brine (5 mL). The combined organic layers were dried over magnesium sulfate and filtered. The solvent was removed using the rotary

evaporator to yield 0.7332 g of product. A small sample of the remaining oil was dissolved in deuterated chloroform and analyzed by proton NMR.

V. *Procedure for the formation of 1,3-Bis(dibenzylamino)propan-2-one Oxime*

In a 25 mL round bottom flask, 1,3-bis(dibenzylamino)propan-2-one (0.500 g, 1.08 mmol) was dissolved in ethanol (7.5 mL) and pyridine (3.25 mL). The solution was treated with hydroxylamine hydrochloride (0.3666 g, 5.27 mmol) and was heated on a steam bath for 2 h. The resulting mixture was concentrated using the rotary evaporator, and the residue was partitioned between 5% aqueous sodium bicarbonate and hexanes. Following the partition, the organic layer was dried over magnesium sulfate and filtered via vacuum filtration. The remaining product was concentrated using the rotary evaporator to yield 0.366 g (71%) of product. A small sample of residue was dissolved in deuterated chloroform and analyzed by proton NMR.

Chapter 3: Results and Discussion

Before discussing the reactions, it is important to note a few points of interest. First, a ^{1}H NMR spectrum of dibenzylamine was taken to compare against future spectra obtained. The ^{1}H NMR of pure dibenzylamine yielded the following NMR shifts: ^{1}H (300 MHz, $CDCl_3$): δ/ppm 1.50 (s, 1H), 3.73 (s, 4H), 7.28 (s, 10H). Also, several of the spectra were obtained from either the 300-MHz or 500-MHz NMR spectrometer due to the 300 MHz machine being inoperable at times. The 500-MHz spectrometer provides stronger resolution.

Reaction I was taken from a paper by Burrows and associates. By reacting chloroacetone and dibenzylamine in THF with triethylamine as base, the authors were able to get an 89% yield of 1-(dibenzylamino)propan-2-one as a pale, yellow oil. The ^{1}H NMR spectrum for my product yielded the following NMR shifts: ^{1}H (300 MHz, $CDCl_3$): δ/ppm 2.13 (s, 4H), 3.22 (s, 2H), 3.70 (s, 4H), 7.40 (s, 10H). Comparing these ^{1}H NMR results to dibenzylamine shows that a reaction did occur, and that dibenzylamine is not present in the product. If dibenzylamine were to be present in the reaction mixture, a singlet peak would be seen at 1.5 ppm with an integration of 1. This was also shown through the TLC taken during the reaction. Throughout the reaction, the TLC showed that the dibenzylamine was slowly dissipating from the reaction mixture, and by hour 40, a spot for the dibenzylamine was no longer present.

After performing this reaction several times, there were subtle differences in the results of Burrows et al. and my results. The original reaction from the literature was done in large quantities for the purpose of their future reactions. The reaction was scaled down to the micromole scale in my work to save materials and make preparation much easier. The major differences between the results was the reaction yields and the appearance of 1-(dibenzylamino)propan-2-one. While the authors reported a yield of 1.186 g (89%), I consistently obtained a yield of 0.121 g (9.07 %). Although these scales look similar, I find it peculiar that the yield percentages are drastically different. Product could have been lost in the rotary evaporator when solvent was being pulled off, or it could have been lost during extractions using the aqueous sodium bicarbonate and brine. Interestingly, 0.409 g of crude product was obtained prior to the purification via the chromatography column, and only 0.121 g was recovered post purification. It is possible that a majority of the yield lost can be attributed to the column. Another possible reason for the low yield is that unreacted dibenzylamine remained after the initial reaction. Left-over dibenzylamine was washed out when the sodium bicarbonate was introduced to the system during extraction. If there was dibenzylamine left unreacted, then the yield would be lower than predicted. The authors also reported that 1-(dibenzylamino)propan-2-one was collected as a pale, yellow oil. After collecting the product from the rotary evaporator, it appeared as a pale, yellow oil as the literature reported; however, after leaving the product in a covered round-bottom flask overnight, the product had become a dark orange solid. To be sure that no other side reactions had occurred, a small amount of solid was dissolved in $CDCl_3$ and examined via ^1H NMR. The spectrum of the solid

was consistent with the original reaction product. This was important to note for attempts at reaction I or reaction II.

Reaction II was the model reaction suggested by Rambabu Sankranti that involves two sequential S_N2 reactions. After following Sankranti's suggested procedure, a product was obtained that yielded the following ^1H NMR chemical shifts: ^1H (500 MHz, $CDCl_3$): δ/ppm 1.29 (t, 0.10H), 2.12 (s, 2H), 2.19 (s, 4H), 3.22 (s, 2H), 3.70 (s, 3H), 4.12 (q, 0.03H), 7.41 (s, 8H). Comparing these values to the chemical shifts from reaction I, the products were determined to be the same due to the presence of chemical shift peaks at 2.19 ppm, 3.22 ppm, 3.70 ppm, and 7.41 ppm. The singlet at 2.12 ppm along with the triplet at 1.29 ppm and quartet at 4.12 ppm belong to ethyl acetate. Ethyl acetate was used during the flash column chromatography, and not all of the ethyl acetate was evaporated off during rotary evaporation. The physical characteristics of the product were also similar because the product came off the rotary evaporator as a pale, yellow oil, but it solidified to a dark orange solid after a while.

Two important differences between reaction I and reaction II were the reaction yields and reaction times. Reaction II yielded 0.8002 g (60%) after purification, which is nearly seven times as much product yielded by reaction I. The Finkelstein reaction can be attributed to this higher yield in my opinion. Under the reaction conditions, the iodine anion from NaI easily displaced the chlorine from chloroacetone. This reaction causes NaCl to precipitate out, thereby yielding an irreversible reaction. Due to the reactivity of iodoacetone, dibenzylamine was easily able to displace the iodine via S_N2 substitution and cause KI to precipitate out due to the presence of K_2CO_3 in the reaction mixture. The presence of K_2CO_3 pushes the S_N2 substitution reaction forward by not only acting as a

base, but also making the reaction irreversible due to the formation of KI as the precipitate. In terms of reaction time, reaction II was much shorter than reaction I. The TLC of reaction II showed that the dibenzylamine had reacted entirely only one and a half hours into the reaction. Reaction II's shorter length of time can also be attributed to the Finkelstein reaction. Chloroacetone has a very high reaction rate when being reacted with NaI in acetone. By replacing acetone, a polar, aprotic solvent, with acetonitrile, another polar, aprotic solvent, it is safe to say that the rate in acetonitrile will be very similar to the rate of the reaction in acetone.

Although the yield and reaction time of reaction II proved that it is the more effective route to obtaining the diamine swallowtails, reaction III was performed to see if anything peculiar occurred that did not show up in the model reactions. Reaction III was performed under two separate sets of conditions: the first being in THF alone and the second being in an 8:2 ratio of THF and water. The purpose of the water in the second set of conditions was to stop the possible side reaction of the formation of an enamine from a ketone and secondary amine. With water being a product of the side reaction, it was thought that the presence of water would force an S_N2 reaction to occur rather than the enamine reaction.

In both set of conditions, triethylammonium chloride was expected to precipitate out of the solution. In the THF-only conditions, solid material was obtained after 40 h of stirring; however, in the THF-water conditions, no solid material was formed after 40 h of stirring. The TLCs for both reactions showed that the dibenzylamine had reacted fully in both solutions. With the lack of precipitate in the THF-water reaction, it is possible that another reaction had taken place due to the presence of water in the solution. The

THF-water reaction yielded the following ^{1}H NMR chemical shifts: ^{1}H (300 MHz, $CDCl_3$): δ/ppm 1.40 (s, 1H), 1.98 (s, 4H), 2.20 (s, 1H), 3.09 (s, 1H), 3.89 (s, 4H), 4.03 (s, 4H), 4.95 (s, 1H), 7.47 (s, 15H). None of these values match the chemical shifts of the starting materials, and it looks as though there are multiple side products that have formed in the solution. By looking at the structure of 1,3-bis(dibenzylamino)propan-2-one, chemical shift estimates for the alpha hydrogens are around 3.5 ppm, and chemical shift estimates for the methylene amino hydrogens are around 4 ppm. The THF-only reaction yielded the following ^{1}H NMR chemical shifts: ^{1}H (300 MHz, $CDCl_3$): δ/ppm 1.98 (s, 5H), 3.89 (s, 9H), 4.95 (s, 1H), 5.29 (s, 0.5H), 7.42 (s, 9H), 7.46 (s, 7H). Similar to the THF-water reaction, the shifts in this spectra do not match the predicted shifts of 1,3-bis(dibenzylamino)propan-2-one. After running the reaction under both sets of conditions several times, I came to the conclusion that both reactions were not forming 1,3-bis(dibenzylamino)propan-2-one. These two reactions may be forming the enamine suggested earlier, or the presence of the second chlorine on the acetone may be causing problems in the reaction that does not allow the targeted S_N2 reaction to occur.

After the multiple failures of reaction III, efforts were shifted to the hopeful success of reaction IV. Based off the observations made from reactions I and II, reaction IV seemed the most feasible option for creating 1,3-bis(dibenzylamino)propan-2-one. Reaction IV yielded a product of 0.7332 g or 16% of the theoretical yield. The product of Reaction IV appeared after rotary evaporation as a dark orange oil, but after cooling to room temperature, the product had solidified into a brownish solid. The product yielded the following ^{1}H NMR chemical shifts: ^{1}H (500 MHz, $CDCl_3$): δ/ppm 3.27 (s, 3H), 3.64 (s, 8H), 7.29 (s, 21H). This NMR was obtained prior to flash column chromatography.

There were no peaks that corresponded to byproducts or starting materials. A small amount of product was purified using flash column chromatography, and an NMR spectrum was obtained for the purified product. The results of the column did not show any major differences from crude NMR. Besides the appearance of ethyl acetate peaks that were predicted, a variety of small peaks did appear post-column; however, the integrations for these small peaks were considered negligible due to the integrations being so small. It was determined that the optimal reaction conditions had been reached prior to column chromatography, and the purification step was deemed unnecessary.

When reaction IV was first attempted, the reaction was only allowed to run for two hours because of the results of reaction II. It was originally thought it would take the same amount of time due to the Finkelstein reaction; however, I did not take into account the time needed to displace both chlorines. When the reaction was only allowed to run for two hours, there was leftover 1,3-dichloroacetone in the reaction mixture. This was apparent due to the scent of 1,3-dichloroacetone in the round-bottom flask after rotary evaporation and the appearance of chemical shift peaks consistent with 1,3-dichloroacetone. With this observation in mind, the reaction was later allowed to run overnight to see if any differences would occur. Allowing the reaction to run overnight seemed to make the reaction reach its optimal conditions because there was no 1,3-dichloroacetone or dibenzylamine present post extraction. The NMR spectrum, as stated before, was very clean and only yielded peaks consistent with the predicted shifts of 1,3-bis(dibenzylamino)propan-2-one.

It should be noted that the product of reaction IV should be used quickly after its formation due to an interesting observation made several days after the product's

formation. The product of reaction IV was left in a tightly sealed and clean round-bottom flask over a weekend. When I came into the lab to start preparing for reaction V, I decided to obtain another NMR spectrum of the product just to be sure nothing had occurred over the time period that elapsed. To my surprise, the ^{1}H NMR of the product yielded the following chemical shifts: ^{1}H (500 MHz, $CDCl_3$): δ/ppm 1.29 (t, 2H), 2.07 (s, 2H), 2.20 (s, 6H), 3.63 (s, 0.5H), 3.69 (1H), 3.87 (s, 2H), 4.15 (q, 1H), 4.29 (s, 1H), 4.44 (s, 1H), 7.31 (s, 17H). The analysis of these chemical shifts shows that the 1,3-bis(dibenzylamino)propan-2-one formed by reaction IV must have degraded over the weekend. The only known shifts from the spectrum are those shifts that correspond to a trace amount of ethyl acetate. It is likely that the shift at 7.31 ppm corresponds to aryl hydrogens, but the other peaks do not correspond to any known peaks from my product. This observation is important for future endeavors dealing with reaction IV. It seems that the product is time-sensitive and degrades after a period of time.

Reaction V is the formation of the oxime from 1,3-bis(dibenzylamino)propan-2-one. Prior to using the procedure from the Wescott-Mattern paper, it was suggested that o-benzylhydroxylamine hydrochloride be used instead of hydroxylamine hydrochloride. According to the paper by Wescott and Mattern, hydroxylamine hydrochloride is the classic reagent used to prepare oximes; however, o-benzylhydroxylamine hydrochloride could be a more effective oxime-producting agent. Time constraints and the lack of o-benzylhydroxylamine hydrochloride led to the abandonment of this avenue, but it would be advantageous for someone to take this avenue in the future.

Using the entirety of the product formed in reaction IV, reaction V produced some interesting results. Reaction V yielded 0.366 g of product or 70.66% of the theoretical

yield. The NMR spectrum contained some confusing results. The product yielded the following ^{1}H NMR chemical shifts: ^{1}H (500 MHz, $CDCl_3$): δ/ppm 3.06 (s, 1H), 3.37 (s, 1H), 3.38 (s, 2H), 3.49 (s, 1H), 3.52 (s, 1H), 3.58 (s, 1H), 3.62 (s, 0.4H), 3.69 (s, 0.2H), 3.82 (s, 4H), 7.35 (s, 24H). At first glance, I concluded that the oxime was not formed; however, after further analyzing the data with Trey Vaughn, a graduate student in the Department of Chemistry and Biochemistry, it is possible that the formation of the oxime caused many spectral changes from the 1,3-bis(dibenzylamino)propan-2-one spectrum such as splitting of peaks. The hydrogen of hydroxylamine could be hydrogen bonding with one of the amine nitrogens of the tails, as shown in Figure 3.1.

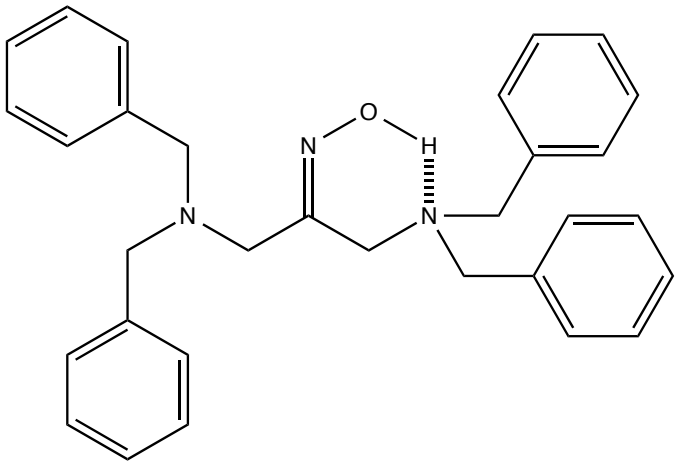

Figure 3.1 – Possible hydrogen-bonding structure of 1,3-bis(dibenzylamino)propan-2-one oxime.

Hydrogen bonding could cause the methylene hydrogens on one side of the molecule to shift differently than the identical methylene hydrogens on the other side of the molecule. Further analysis is required to determine whether the product obtained is the targeted oxime.

A problem that occurred during reaction V was the solid formed by 1,3-bis(dibenzylamino)propan-2-one and hydroxylamine hydrochloride would not dissolve in

a number of solvents that worked with 1,3-bis(dibenzylamino)propan-2-one. Prior to the partition with sodium bicarbonate and hexanes, the product needed to be dissolved in a solvent. The product from reaction IV was soluble in ethyl acetate, dichloromethane, acetonitrile, chloroform, and THF. The product from reaction V would not dissolve in ethyl acetate, hexanes, dichloromethane, acetonitrile, chloroform, or THF. After several trial-and-error attempts, the reaction V product finally dissolved in a mixture of acetonitrile and THF. This seems particularly odd because neither solvent alone would dissolve the solid. The success of polar, aprotic solvents in the past would make one think that either of these solvents alone would dissolve the solid.

Chapter 4: Conclusion

Although the main goal of this research was not fulfilled, the results thus far are promising for future endeavors into the synthesis of the diamino swallowtails. By far, the hardest step in this research was the creation of 1,3-bis(dibenzylamino)propan-2-one because of the lack of literature information dealing with this reaction. It would be wise for future chemists to study ways to increase the yield of 1,3-bis(dibenzylamino)propan-2-one. With only a 16% experimental yield, it is disconcerting knowing that 84% of product is unaccounted for with no byproducts being created based on ^{1}H NMR data. A personal recommendation would be to analyze the precipitates formed. It may be possible that the solids formed are absorbing product as they sit in the reaction mixture. If this were the case, extra steps should be taken to ensure that the product is completely washed of the desired product. This can be done by washing the solid with excess solvent to wash out any remaining product that is on the precipitates. Also it would be beneficial to determine how to optimize the creation of the oxime. Looking back on the questionable results of reaction V, the problem may lie in the heating of the reaction. After speaking with another student who has worked with oxime reactions, the oxime may not be forming properly if the reaction mixture is not constantly heated.

If the creation of the oxime were successful, the next step would be the reduction of the oxime into an amine. This reaction should run relatively simple using a similar procedure from the paper by Wescott and Mattern. Their reaction involves reacting the oxime with sodium bis(2-methoxyethoxy)aluminum hydride (RedAl) in toluene under

reflux. The only reservation I have with this reaction is the use of HCl to dissolve the RedAl products during workup. The use of a strong acid could protonate our target amine, which would end up causing the amine to stay in the aqueous layer upon extraction. If this were to happen, it would make extracting the amine more difficult. After the creation of the amine, the next step would be the creation of the target molecule of this research. With the knowledge gained thus far and more time in the future, I am confident that the target molecule of this research can be created with hopes of answering questions regarding the complexities of PBI binding in G-quadruplex DNA.

References

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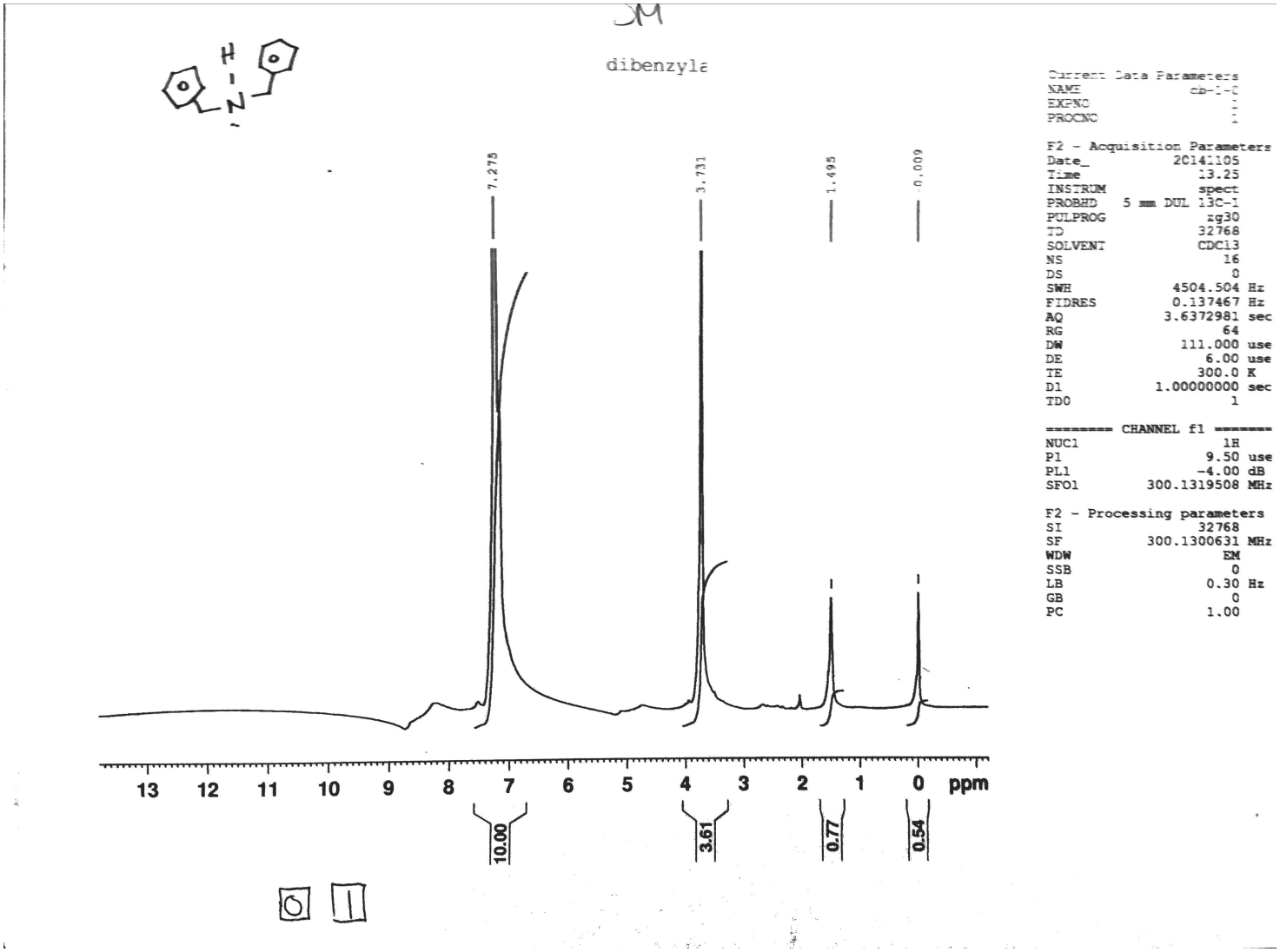
Supplemental Data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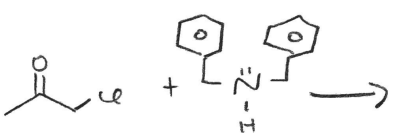

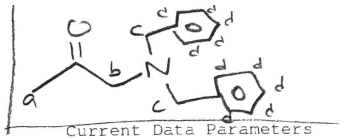

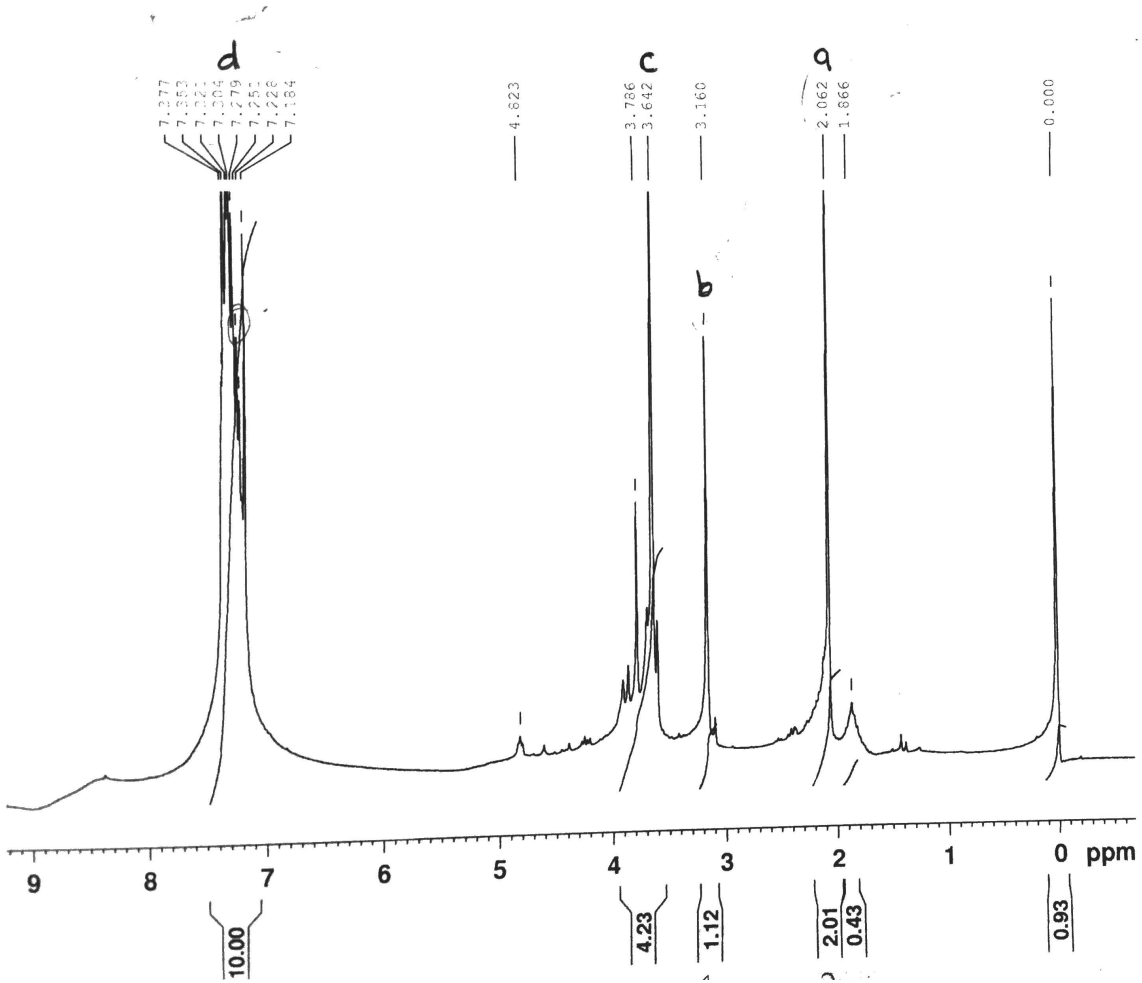

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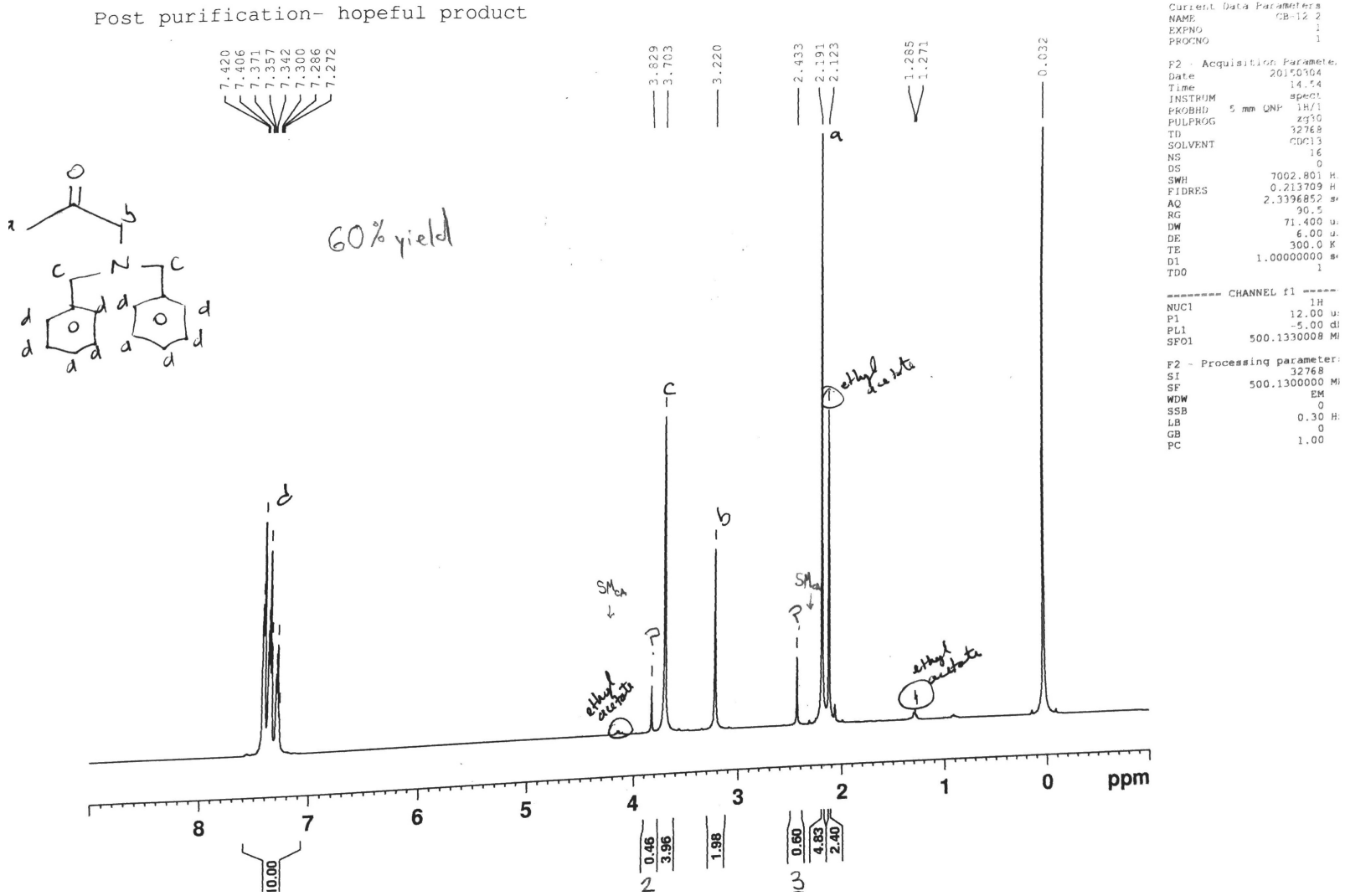

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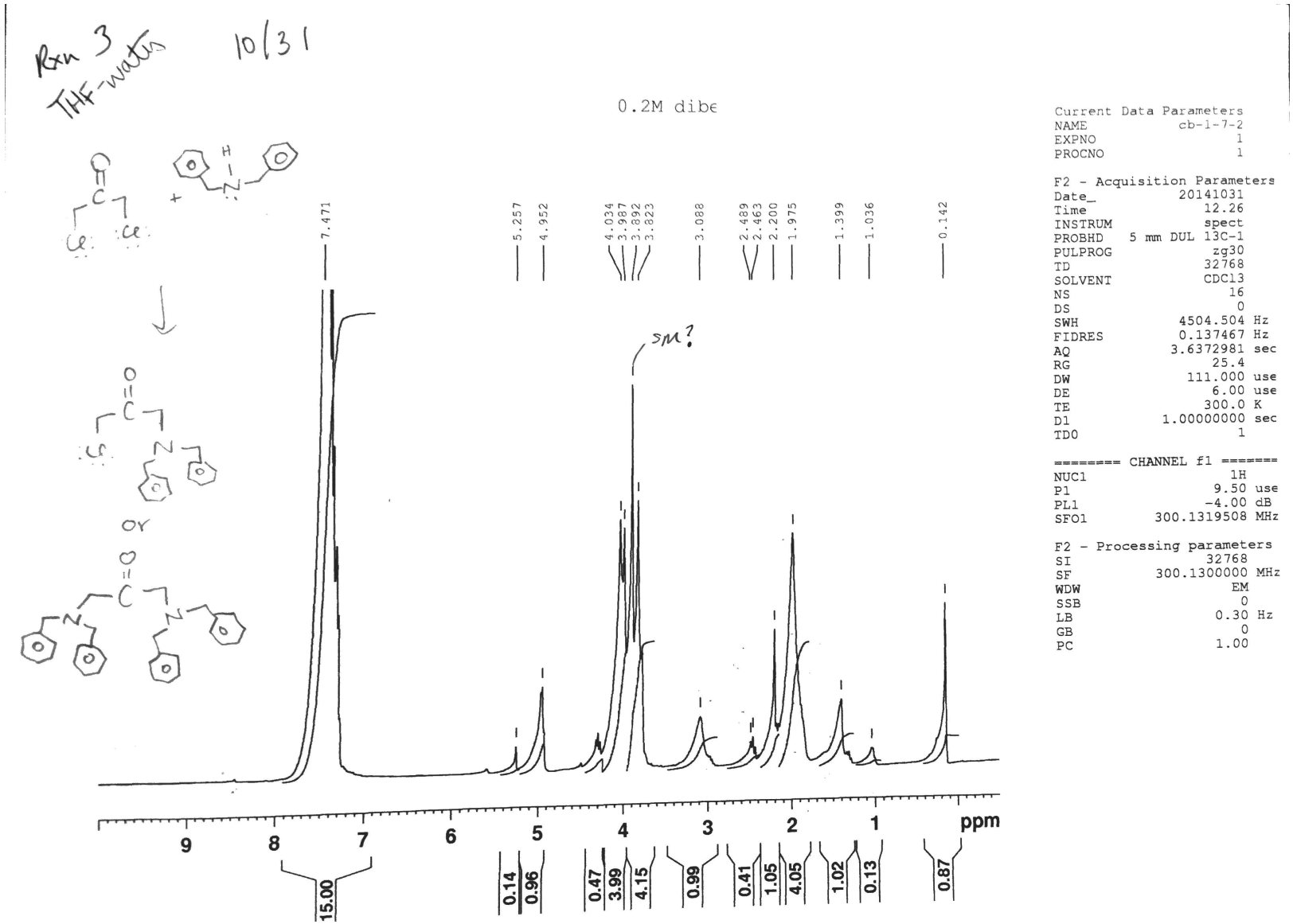


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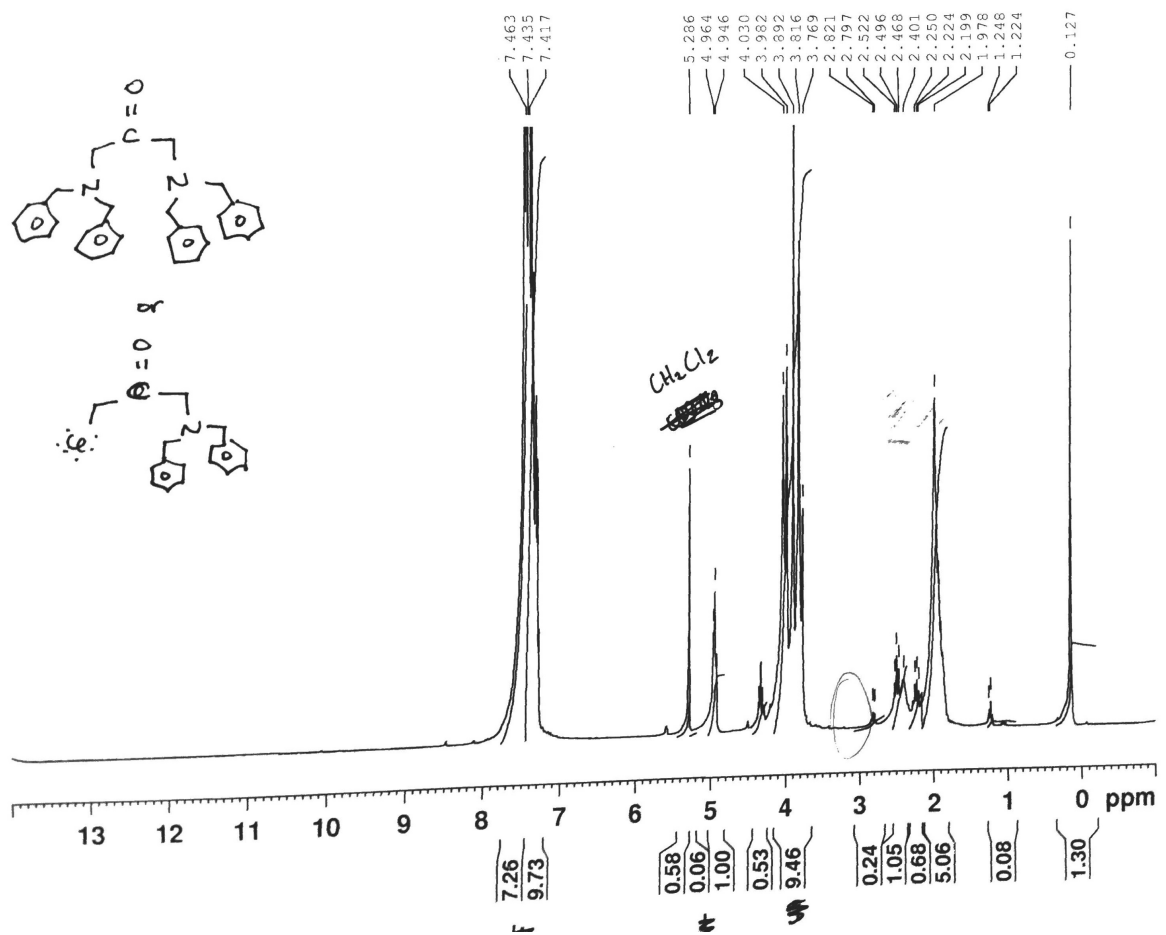


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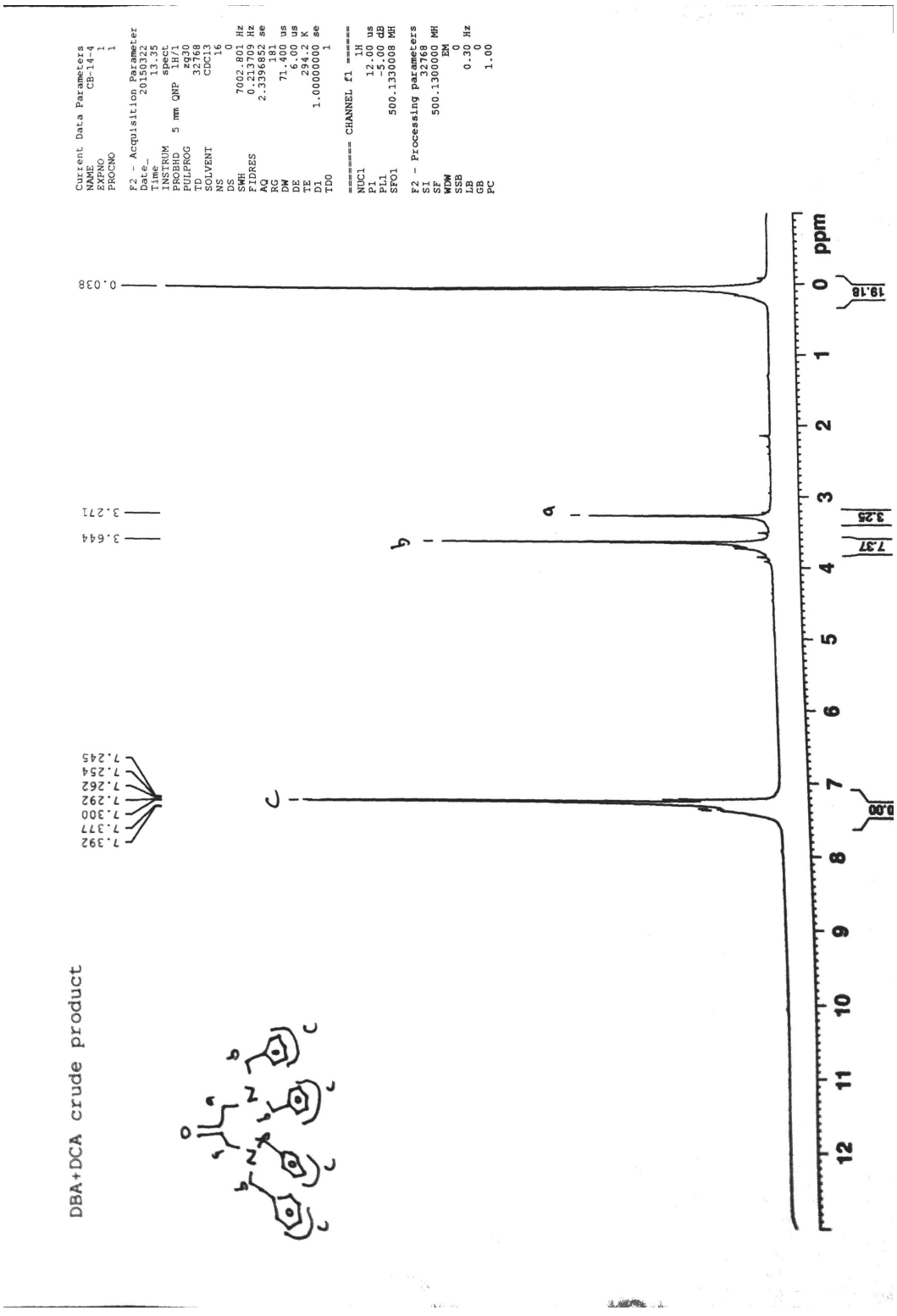
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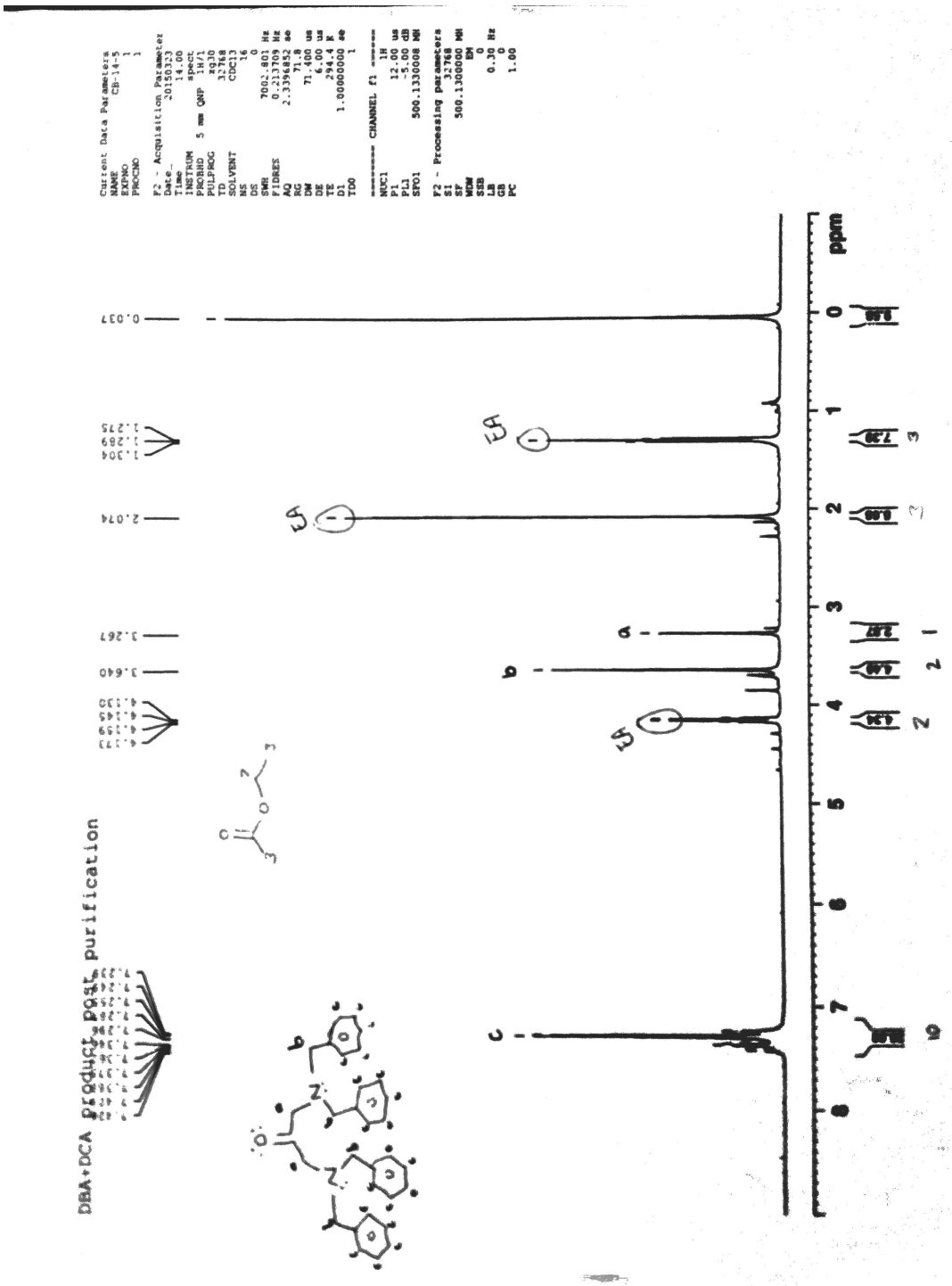
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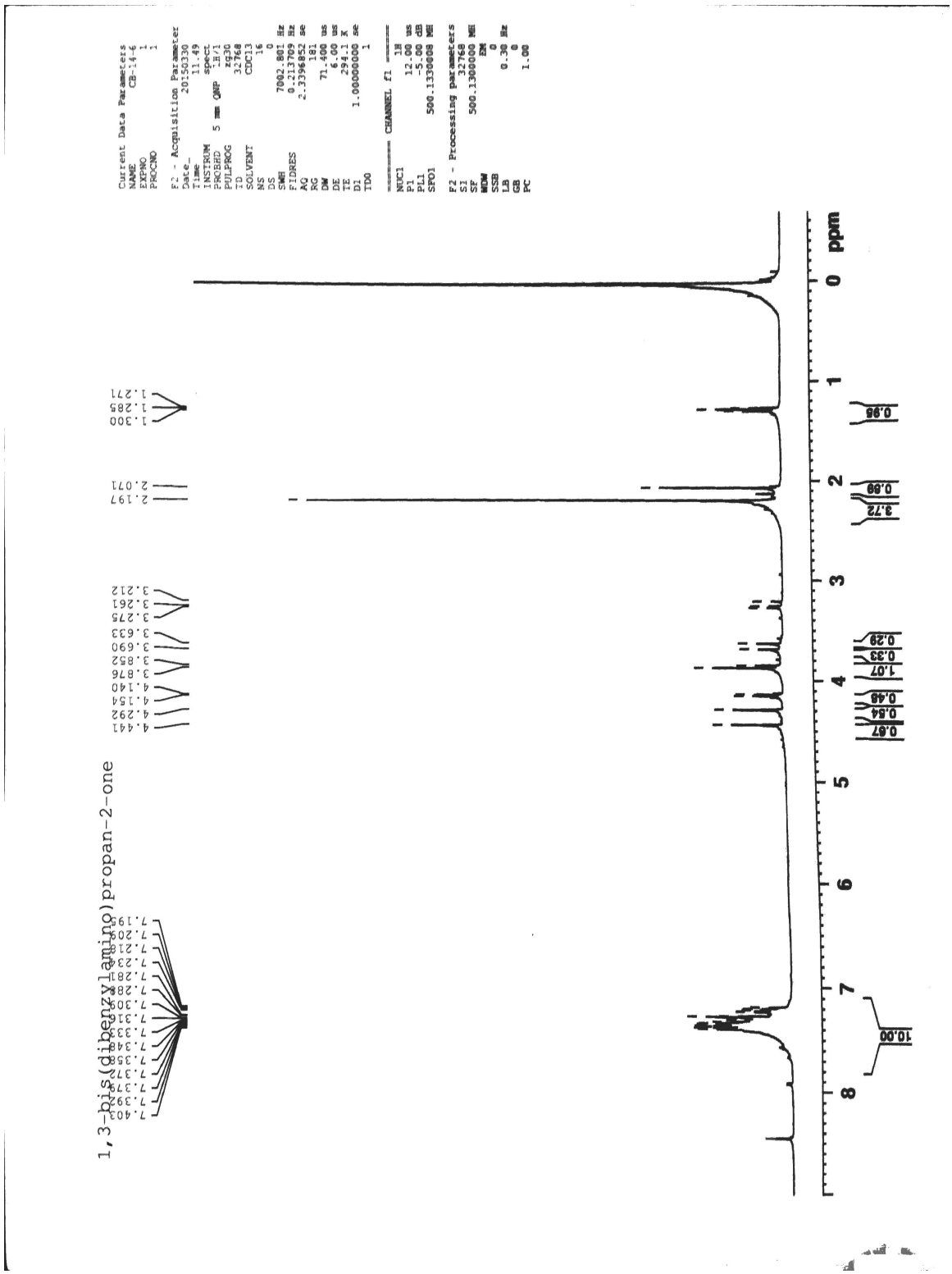
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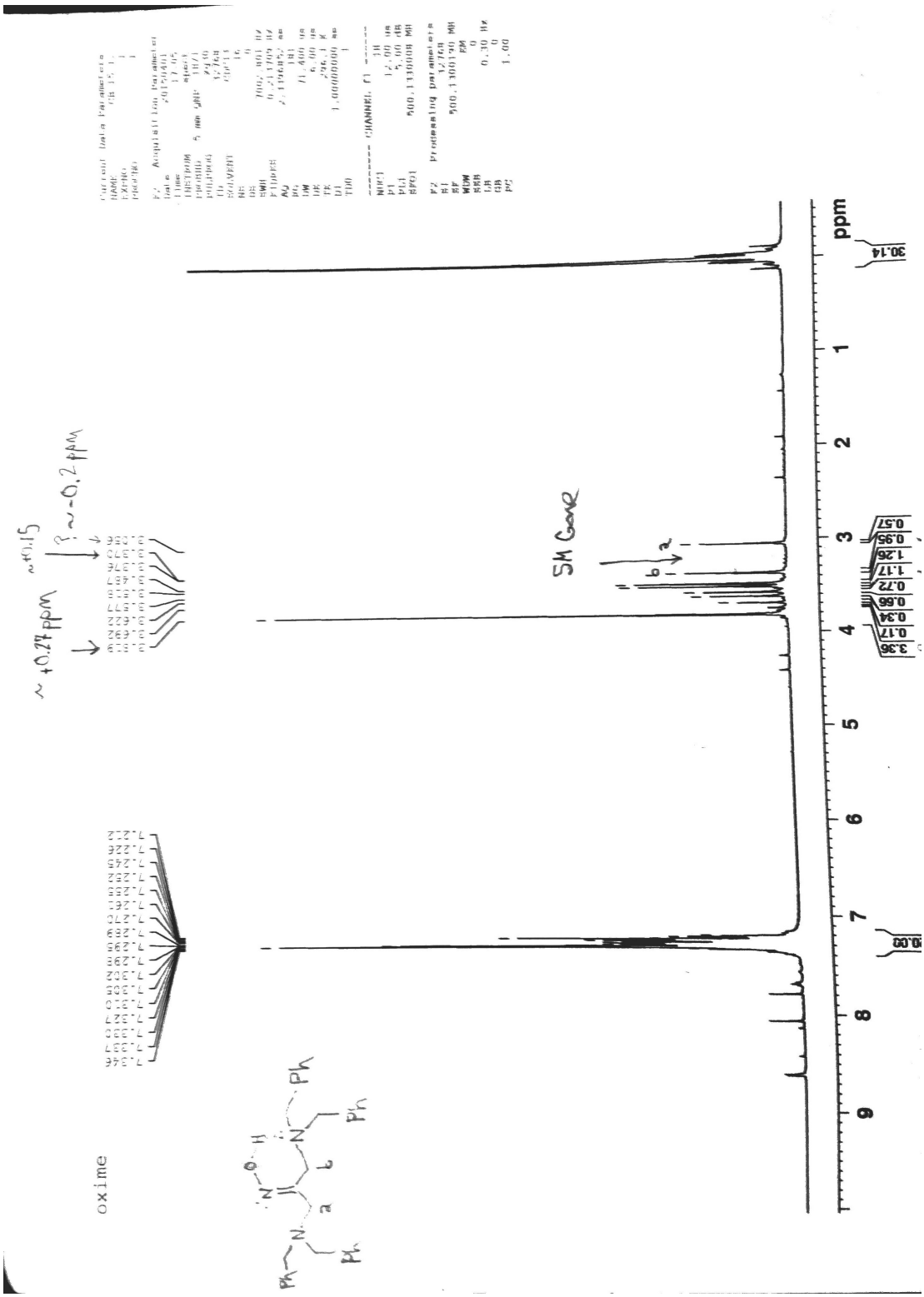
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